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SELENIUM DIOXIDE MEDIATED BENZYLIC sp^3 C–H OXIDATION IN ACETIC ACID: SYNTHESIS OF LOPHINE DERIVATIVES FROM α-METHYLENE KETONES *VIA* A DOMINO MULTICOMPONENT REACTION

Vineet Jeena* and Mncedisi Mazibuko

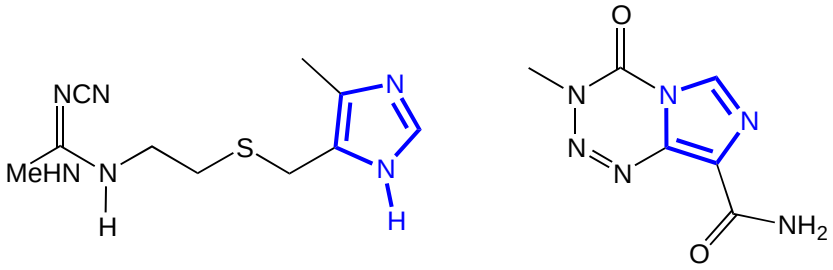
School of Chemistry and Physics, University of KwaZulu-Natal, Scottsville, Pietermaritzburg, 3209, South Africa; E-mail: Jeenav1@ukzn.ac.za

Abstract – We report a selenium dioxide/acetic acid catalysed one-pot conversion of α-methylene ketones to 1,2-diaryldiketones as a key step to successfully access lophine derivatives in a domino multicomponent reaction.

Domino reactions, also referred to as cascade or zipper reactions have emerged as a powerful tool in organic chemistry as they allow for the formation of complex molecules in an economical and ecologically acceptable way with high yields in short reaction times, ultimately resulting in a more efficient synthesis.[1] The most renowned domino reaction is the tandem oxidation process (TOP), pioneered by the Taylor research group, which involves mixing an alcohol, nucleophile and oxidant in a one-pot synthesis to produce a smorgasbord of synthetically useful compounds.[2] This area of research has been well studied and numerous reviews on this topic have been compiled indicative of its importance in the current synthetic chemistry landscape.[3]

Given the popularity of the TOP, we sought to develop a new type of domino reaction and explored the oxidation of the C–H bond to produce diketone derivatives which could be reacted with a nucleophile to produce the target compound. This methodology has been used to generate quinoxalines by trapping the generated 1,2-diaryldiketone with *o*–phenylenediamine as part of a simple, one-pot synthesis.[4] However, we were intrigued by the possibility of a C–H oxidation to produce the 1,2-diaryldiketone which could set off a chain of reactions, culminating in the desired product.

Imidazoles are known to possess a number of biological applications and are present, as the skeletal structure, in a wide range of bioactive molecules (Figure 1).[5]

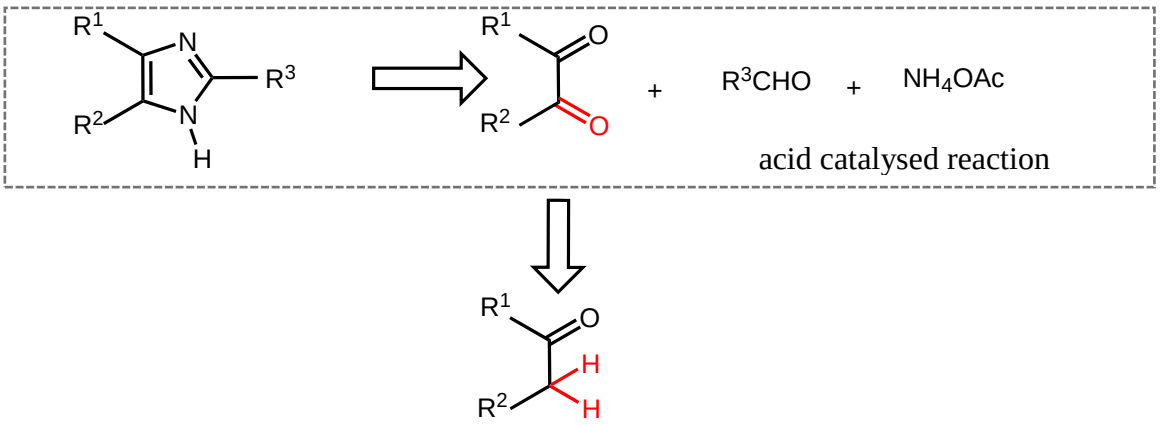


Cimetidine Temozolomide

Figure 1. Imidazole skeletal structure in bioactive molecules

2,4,5–Triphenyl-1*H*-imidazole or lophine, and its derivatives, in particular, have shown numerous interesting properties such as chemiluminescence[6] with one of the first chemiluminescence reactions being the autoxidation of lophine reported in 1877 by Radziszewski.[7] In addition, lophine and its derivatives have also found application as fiber[8] and fluorescent sensors.[9] From a medicinal chemistry perspective, lophine fused tacrine hybrids have shown promising activity as acetylcholinesterase (AchE) and butyrylcholinesterase (BuChE) inhibitors which may be a potential approach to treat Alzheimer's disease[10] while, lophine derivatives have also shown promising activity as α-glucosidase inhibitors which could be exploited to treat diabetes.[11]

The most common route to access these elegant compounds is using a diketone, aldehyde and ammonium acetate under metal or acid catalysis, however, in many cases these catalysts are elaborate and expensive.[12] In addition, many α-diketones are not commercially vailable and need to be synthesised using complex processes.[13] Hence, the use of simple ketones rather than the traditional α-diketone would be a more attractive strategy to access imidazoles.[14]



Scheme 1. The proposed synthetic strategy to imidazole derivatives using benzylic sp^3 C–H oxidation as a key step

Cognisant of the importance of lophine derivatives in synthetic and medicinal chemistry, we aimed to develop a new route to these compounds using a sp^3 C–H oxidation as a key step. As part of our goal, we

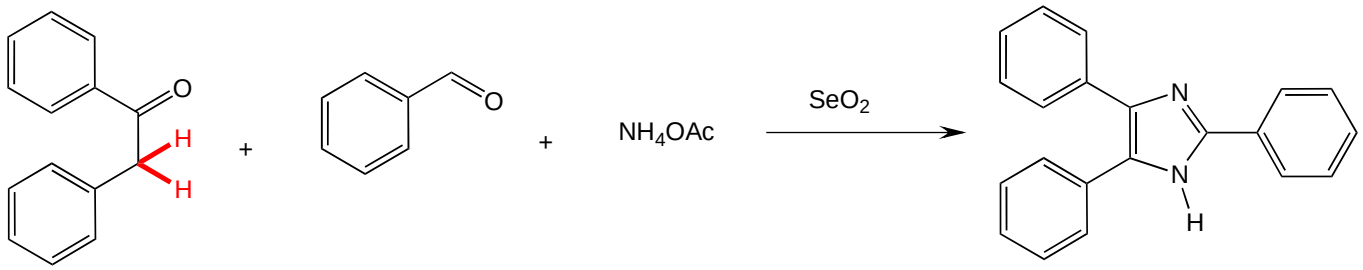
hoped to commence from the α–methylene ketone which could be converted to the 1,2-diaryldiketone, using C–H oxidation, and in the presence of an aldehyde and ammonium acetate under acidic conditions, descend to the imidazole in a one-pot synthesis (Scheme 1).

Our proposed route presented two initial challenges: (i) we needed to judiciously choose a reagent to generate the 1,2-diaryldiketone through the oxidation of α-methylene ketones and (ii) select an appropriate catalyst to create an environment conducive to the coupling reaction. With regards to our first objective, in the last five years, a number of innovative system for the oxidation of α-methylene ketones have been reported such as $Cu(OAc)_2/Ph_3P$,[15a] $Cu(OAc)_2{\cdot}H_2O/K_2CO_3$,[4c] $DMSO/KHCO_3$,[15b] $Pd(OAc)_2$/triazole ligand[15c] and KO^{t}Bu/18-Crown-6/O_2.[15d] Some of these systems use basic additives or require the synthesis of complex ligands which renders them moot for our study. However, our attention was drawn to the use of selenium dioxide as this reagent is well known in the synthetic organic chemistry community[16] and since the pioneering reports of Corey[17a] and Sharpless,[17b] selenium dioxide has reliably been used to generate diketones in high yields *via* the oxidation of α–methylene ketones.[18] Additionally, there has been an initiative to introduce the eco-friendly aspects of organoselenium chemistry through the use of alternative greener solvents, bioinspired organoselenium catalysts and the use of non-conventional and energy saving sources of activation.[19] Thus, the use of selenium in a domino, one-pot syntheses would be an additional cog to this ever-expanding initiative. To achieve our second goal of generating an acidic environment, we proposed two possible approaches, namely the use of known imidazole catalysts in commonly employed organic solvents or the use of an acidic solvent which could serve as a reaction medium and catalyst.

Our optimisation study commenced by monitoring the coupling of 2-phenylacetophenone **1a**, benzaldehyde **2a** and ammonium acetate under various reaction conditions to produce the product 2,4,5-triphenyl-1*H*-imidazole **3a** and the results are summarised in Table 1.

Firstly, the use of traditional, readily available, organic solvents only were evaluated, and under these conditions, no significant product was detected (**Table 1**, **entries 1-3**) with only trace amounts detected when toluene was used as a solvent. Next, we aimed to encourage the formation of the product by using known catalysts for the synthesis of imidazoles. The reactions were conducted in toluene with Montmorillonite K10[20a] and silica gel[20b] as the catalysts of choice as they are readily available and eco-friendly. This approach also failed to produce any significant product (**Table 1**, **entries 4-5**).

Table 1. Optimisation of reaction conditions for the formation of 2,4,5-triphenylimidazole from 2-phenyl–acetophenone *via* a domino multicomponent reaction[a]



1a **2a** **3a**

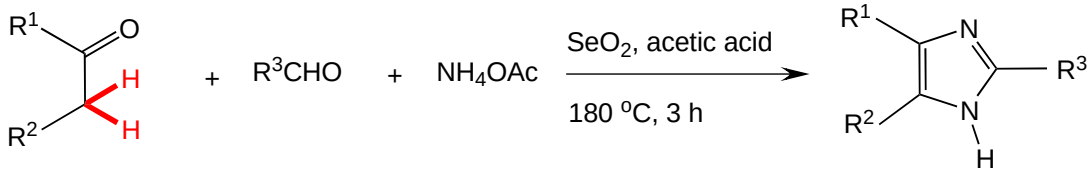
Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	–	PhMe	110	trace
2	–	EtOH	78	0
3	–	MeCN	82	0
4	Montmorillonite K10	PhMe	110	trace
5	silica gel	PhMe	110	trace
6	–	HCl	100	0
7	–	H_2SO_4	100	10
8	–	HNO_3	100	10
9	–	AcOH	rt	0
10	–	AcOH	120	68
11	**–**	**AcOH**	**180**	**83**
12[c]	–	AcOH	180	0

[a] Reaction conditions: 2-phenylacetophenone (0.5 mmol), benzaldehyde (0.5 mmol), ammonium acetate (5.0 mmol) and SeO_2 (0.5 mmol) were reacted for 3 h (see ESI for full details). [b] Isolated yield.
[c] Without SeO_2.

We moved on to our second strategy which comprised of the use an acid to serve as a reaction medium and catalyst. In this case, commonly used mineral acids HCl, H_2SO_4 and HNO_3 (**Table 1**, **entries 6-8**) were employed but, once again, no significant amount of product was detected. The use of acetic acid produced no product at room temperature (**Table 1**, **entry 9**) but when the temperature was increased to 120 °C the desired product was, to our delight, isolated in a yield of 68% (**Table 1**, **entry 10**). We postulated that a further increase in temperature would result in a higher yield. In order to carry out the reaction at an elevated temperature, a specially designed cylindrical tube was used to safely carry out the reaction and prevent loss of reagents (See ESI for details). The reaction temperature was increased to 180 °C and, under these conditions; the desired imidazole was isolated in a good yield of 83% (**Table 1**, **entry 11**). The use of

selenium dioxide was found to be essential for this reaction as, in its absence, no product was formed (**Table 1**, **entry 12**). With the optimised conditions in hand, we sought to explore the scope and limitations of the devised system by varying the reactants and the results of which are described in Table 2.

Table 2. Synthesis of lophine derivatives using α–methylene ketones, aldehydes and ammonium acetate[a]



Entry	R^1	R^2	R^3	Yield (%)[b]
1	Ph	Ph	Ph	**3a** (83)
2	Ph	Ph	4-ClC_6H_4	**3b** (77)
3	Ph	Ph	4-BrC_6H_4	**3c** (73)
4	Ph	Ph	4-FC_6H_4	**3d** (84)
5	Ph	Ph	4-(MeO)C_6H_4	**3e** (87)
6	Ph	Ph	4-MeC_6H_4	**3f** (83)
7	Ph	4-ClC_6H_4	Ph	**3g** (82)
8	Ph	4-ClC_6H_4	4-ClC_6H_4	**3h** (74)
9	Ph	4-ClC_6H_4	4-BrC_6H_4	**3i** (87)
10	Ph	4-ClC_6H_4	4-(MeO)C_6H_4	**3j** (61)
11	Ph	4-ClC_6H_4	4-FC_6H_4	**3k** (76)
12	Ph	Ph	2-(MeO)C_6H_4	**3l** (88)
13	Ph	Ph	2-FC_6H_4	**3m** (83)
14	Ph	Ph	2-$NO_2C_6H_4$	**3n** (83)
15	Ph	Ph	3-$NO_2C_6H_4$	**3o** (51)
16	Ph	Ph	furan-2-yl	**3p** (67)
17	Ph	Ph	cyclohexyl	**3q** (83)[c]
18	Me	Me	Ph	**3r** (nd)[d]

[a] Reaction conditions: α-Methylene ketone (0.5 mmol), aldehyde (0.5 mmol), ammonium acetate (5.0 mmol) and SeO_2 (0.5 mmol) in 3 mL glacial acetic acid. [b] Isolated yields reported. [c] One-pot conditions. [d] Not determined.

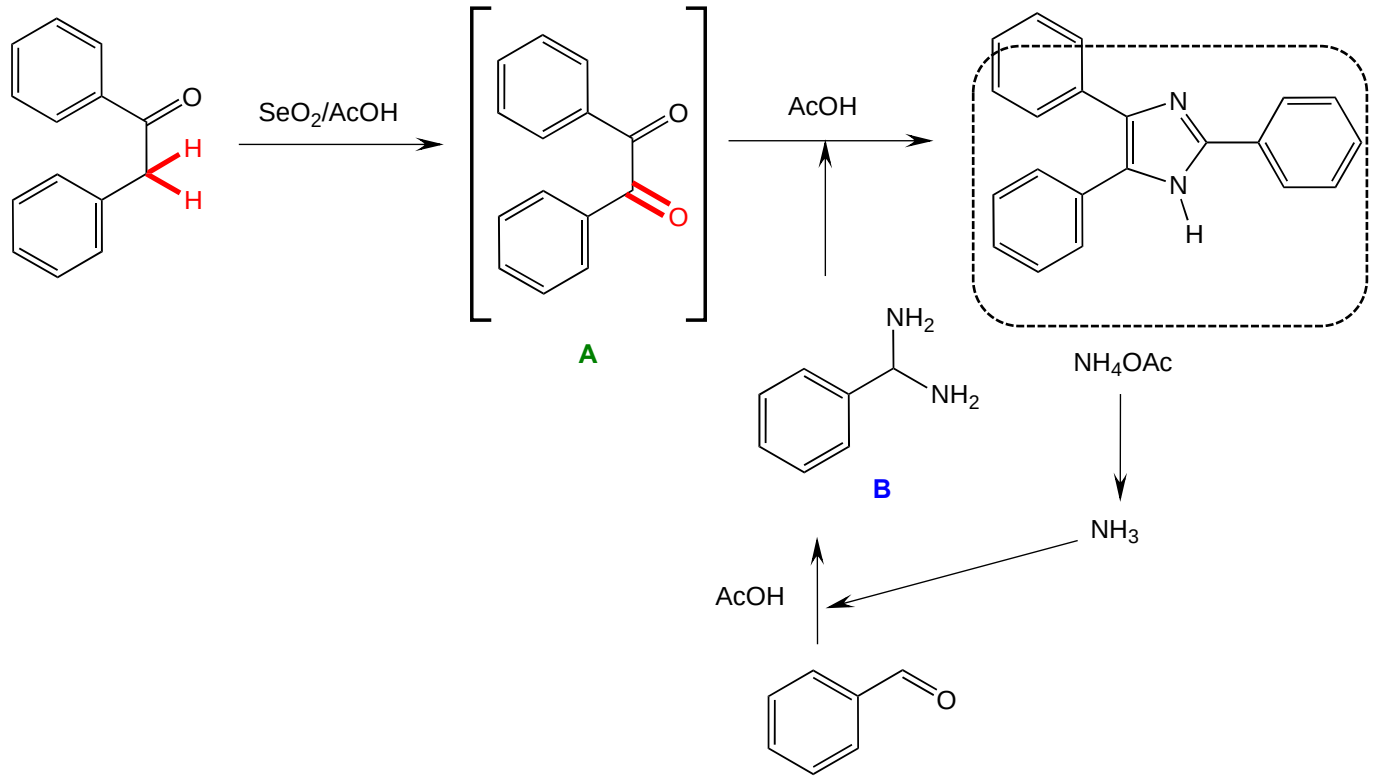
After the successful synthesis of lophine (**Table 2**, **entry 1**), we commenced the library synthesis with a variation of the aldehyde with substituents at the 4-position. The use of *para*-substituted benzaldehydes produced the desired products in good yields of 73-87% regardless of whether electron donating or electron

withdrawing substituents were used (**Table 2**, **entries 2-6**). The use of a substituted 2-phenylacetophenone derivative also produced the desired imidazoles in moderate to good yields in the presence of various *para*-substituted aldehydes (**Table 2**, **entries 7-11**). While this system was efficient using electron-donating groups (EDGs) and electron-withdrawing groups (EWGs), the presence of an EDG group such as the –OMe resulted in a lower yield (61% in the case of the –OMe substituent). Next, the use of *ortho*-substituted aldehydes such as the methoxy, fluoro and nitro substituents produced the desired product in good yields **(Table 2**, **entries 12-14)** while the use of a *meta*-substituted aldehyde also resulted in the desired product albeit in a moderate yield of 51% (**Table 2**, **entry 15**). The operational simplicity of the developed method is remarkable as (i) the elemental selenium is easily removed by filtration and (ii) upon pouring the mixture into an ammonia solution, the product immediately precipitated to deliver spectroscopically pure imidazole.

While our study was directed toward lophine derivatives, in particular, due to their amazing properties (*vide supra*) we briefly extended the study towards other substituents. The use of a variation heterocyclic aldehyde such as furfural resulted in the desired product in a yield of 67% (**Table 2**, **entry 16**). Next, we turned our attention to the use of a aliphatic aldehyde as a coupling partner. The use of cyclohexane–carboxaldehyde resulted in no product, probably due to the susceptibility of the cyclohexane ring to attack by selenium dioxide.[16a] To support this hypothesis, the reaction was repeated with phenylacetophenone and selenium dioxide only, followed by the addition of cyclohexanecarboxaldehyde and ammonium acetate and under these conditions the desired product was isolated in a yield of 83% (**Table 2**, **entry 17**). However, the developed system was not applicable to aliphatic α-methylene ketones as no product was detected when 2-butanone was used as a starting material (**Table 2**, **entry 18**).

Based on previous literature reports,[21] a mechanistic explanation for the formation of the substituted imidazoles is proposed (Scheme 2).

In the presence of acetic acid, 2–phenylacetophenone is oxidised to produce the 1,2-diaryldiketone **A** by selenium dioxide. Concurrently, the aldehyde reacts with ammonium acetate to produce the imine intermediate **B**. This intermediate undergoes cyclocondensation with the 1,2-diaryldiketone to produce the final imidazole. Thus, acetic acid plays a crucial role in this reaction as it (i) promotes the oxidation of the α-methylene ketone to the diketone in the presence of selenium dioxide[17a] and (ii) catalyses the three component coupling reaction between the generated diketone, aldehyde and ammonia to produce the desired imidazole.[21a]



Scheme 2. Proposed reaction mechanism for the SeO_2/acetic acid mediated imidazole synthesis

In summation, a simple and efficient procedure for the one-pot imidazole synthesis from the reaction of α-methylene ketones instead of the traditional diketone is described. Using a stoichiometric amount of selenium dioxide in the presence of acetic acid, a wide range of α-methylene ketones were oxidised to the 1,2-diaryldiketone which were directly engaged in a three-component imidazole synthesis in moderate to good yields. A mechanism for the formation of the desired imidazoles is proposed in order to rationalise the product formation. Further studies expanding the scope of this methodology as well as in-depth mechanistic studies are currently underway in our laboratories and will be reported in due course.

EXPERIMENTAL

All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance 400 operating at either 400 or 100 MHz using DMSO-d_6 as an internal standard. Chemical shifts are expressed in parts per million (ppm) relative to the residual solvent and coupling constants (*J* values) were recorded in Hz. High-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. IR spectra were recorded on Perkin Elmer FTIR Spectrometer. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using Kofler hot-stage melting apparatus. All reagents that were used are commercially available.

Typical Procedure for the Preparation of 2,4,5- Trisubstituted Imidazoles (3).

2,4,5-Triphenylimidazole (3a). 2-Phenylacetophenone (98.12 mg, 0.5 mmol), selenium dioxide (55.48 mg, 0.5 mmol), ammonium acetate (385.4 mg, 5.0 mmol), and benzaldehyde (51.02 µL, 0.5 mmol) were mixed in an elongated tube (equipped with a reflux condenser) with 5.00 mL glacial acetic acid and stirred for 3 h at 180 ºC. After cooling, the reaction mixture was added drop-wise into a 25% ammonia solution at 0 ºC to form a white precipitate which was then filtered and dried in oven at 50 ºC for 4 h to afford 2,4,5-triphenylimidazole as a white solid (123.30 mg, 83%); mp 271 – 273 ºC. IR (cm^{-1}): 3426, 2855, 1600, 1488; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 8.12 (d, J = 7.84 Hz, 2H), 7.62 (d, J = 8.08 Hz, 2H), 7.55 (d, J = 7.25 Hz, 2H), 7.51 – 7.44 (m, 4H), 7.39 (t, J = 7.46 Hz, 2H), 7.32 (t, J = 7.46 Hz, 2H) 7.24 (t, J = 7.66 Hz, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 146.0, 137.7, 135.7, 131.6, 130.9, 129.1, 128.9, 128.7, 128.7, 127.2, 127.6, 126.9, 125.7; HRMS (ESI) calcd for $C_{21}H_{16}N_2$ $[M + H]^+$ 297.1392, found 297.1388. Data consistent with literature.[22,26,27]

2-(4-Chlorophenyl)-4,5-diphenylimidazole (3b): a white solid; mp 258 – 261 ºC; IR (cm^{-1}): 3423, 3059, 1602, 1324; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.12 (d, J = 8.57 Hz, 2H), 7.56 (d, J = 8.57 Hz, 6H), 7.38 (s, 6H); ^{13}C (100 MHz, DMSO-d_6) δ 144.9, 133.3, 129.9, 129.8, 129.7, 129.3, 129.2, 129.0, 128.8, 128.3, 127.6, 127.3; HRMS (ESI) calcd for $C_{21}H_{15}N_2Cl$ $[M + H]^+$ 331.1002, found 331.1009. Data consistent with literature.[22]

2-(4-Bromophenyl)-4,5-diphenylimidazole (3c): a white solid; mp 255 – 258 ºC; IR (cm^{-1}): 3408, 3060, 1601, 1323; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.06 (d, J = 8.42 Hz, 2H), 7.70 (d, J = 8.61 Hz, 2H), 7.55 (d, J = 7.14 Hz, 4H), 7.38 (s, 6H); ^{13}C (100 MHz, DMSO-d_6) δ 144.9, 137.8, 135.5, 132.1, 131.5, 130.0, 129.8, 129.4, 128.9, 127.6, 121.9; HRMS (ESI) calcd for $C_{21}H_{15}BrN_2$ $[M + H]^+$ 375.0497, found 375.0500. Data consistent with literature.[22]

2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3d): a fawn solid; mp 249 – 253 ºC; IR (cm^{-1}): 3408, 3029, 1608, 1492, 1221, 1159, 1131, 694; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.14 (q, J = 5.59 Hz, 2H), 7.55 (d, J = 6.88 Hz, 4H), 7.36 – 7.31 (m, 8H); ^{13}C (100 MHz, DMSO-d_6) δ 163.8, 161.4, 145.2, 137.6, 135.6, 131.5, 129.1, 128.9, 128.7, 128.3, 127.8, 127.8, 127.5, 127.5, 127.0, 116.2, 116.0; HRMS (ESI) calcd for $C_{21}H_{15}FN_2$ $[M + H]^+$ 315.1298, found 315.1307. Data consistent with literature.[23,24]

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3e): a pale-white solid; mp 226 – 229 ºC; IR (cm^{-1}): 3400, 3027, 1613, 1492, 1174; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.03 (d, J = 9.13 Hz, 2H),

7.56 – 7.51 (d, *J* = 13.52, 4H) 7.44 – 7.23 (m, 6H), 7.07 (d, *J* = 8.73 Hz, 2H), 3.83 (s, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 159.9, 146.1, 137.3, 135.8, 131.7, 129.1, 128.8, 128.6, 128.1, 128.1, 127.5, 127.2, 126.9, 123.7, 114.6, 55.7; HRMS (ESI) calcd for $C_{22}H_{18}N_2O$ $[M + H]^+$ 327.1497, found 327.1494. Data consistent with literature.[22,23]

4,5-Diphenyl-2-(*p*-tolyl)-1*H*-imidazole (3f): a pale white solid; mp 230 – 232 ºC; IR (cm^{-1}): 3394, 3029, 1603, 1486, 1321; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.74 (t, *J* = 4.23 Hz, 1H), 7.59 – 7.52 (q, *J* = 7.40 Hz, 4H), 7.46 – 7.42 (t, *J* = 7.16 Hz, 2H), 7.34 – 7.29 (m, 6H), 7.24 – 7.22 (d, *J* = 7.24 Hz, 1H), 2.66 (s, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 146.6, 137.1, 136.8, 135.9, 131.7, 131.6, 130.5, 129.2, 129.1, 128.8, 128.7, 128.6, 128.1, 127.9, 127.5, 126.9, 126.2, 21.6; HRMS (ESI) calcd for $C_{22}H_{18}N_2$ $[M + H]^+$ 311.1548, found 311.1554. Data consistent with literature.[22,24]

5-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3g): a white solid; mp 241 – 245 ºC; IR (cm^{-1}): 3415, 3055, 1600, 1322; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.10 (d, *J* = 7.79 Hz, 2H), 7.55 – 7.38, (m, 12H); ^{13}C (100 MHz, DMSO-d_6) δ 146.4, 146.2, 138.2, 136.3, 135.5, 134.5, 132.7, 131.5, 131.3, 130.7, 130.5, 130.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 127.7, 127.4, 127.2, 125.7; HRMS (ESI) calcd for $C_{21}H_{15}ClN_2$ $[M + H]^+$ 331.1002, found 331.1007. Data consistent with literature.[25]

2,5-Bis(4-chlorophenyl)-4-phenyl-1*H*-imidazole (3h): a white solid; mp 249 – 252 ºC; IR (cm^{-1}): 3419, 3063, 1600, 1311; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.10 (d, *J* = 8.66 Hz, 2H), 7.56 – 7.37 (m, 11H); ^{13}C (100 MHz, DMSO-d_6) δ 145.2, 133.4, 129.5, 129.3, 129.1, 128.8, 127.4; HRMS (ESI) calcd for $C_{21}H_{14}N_2Cl_2$ $[M + H]^+$ 365.0612, found 365.0615.

2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (3i): a white solid; mp 248 – 250 ºC; IR (cm^{-1}): 3416, 3064, 1600, 1323; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.04 (d, *J* = 9.00 Hz, 2H), 7.69 (d, *J* = 8.53 Hz, 2H), 7.54 – 7.36 (m, 9H); ^{13}C (100 MHz, DMSO-d_6) δ 145.2, 132.2, 129.9, 129.1, 128.9, 127.6, 122.0; HRMS (ESI) calcd for $C_{21}H_{14}BrClN_2$ $[M + H]^+$ 409.0107, found 409.0117.

5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (3j): a white solid; mp 233 – 237 ºC, IR (cm^{-1}): 3408, 3060, 2289, 1601, 1220; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.01 (d, *J* = 8.21 Hz, 2H), 7.57 – 7.44 (m, 6H), 7.41 – 7.27 (m, 3H), 7.07 (d, *J* = 8.21 Hz, 2H), 3.83 (s, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 160.0, 146.3, 137.9, 135.9, 135.6, 134.7, 132.5, 131.5, 131.3, 130.3, 129.2, 129.0, 128.9, 128.7, 128.3, 127.8, 127.3, 123.5, 114.6, 55.7; HRMS (ESI) calcd for $C_{22}H_{17}ClN_2O$ $[M + H]^+$ 361.1108, found 361.1097.

5-(4-Chlorophenyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole (3k): a cream white solid; mp 245 – 249 °C; IR (cm^{-1}): 3431, 3062, 1488, 1222, 1159, 1129, 698; ^1H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.13 (q, J = 5.58 Hz, 2H), 7.56 – 7.52 (t, J = 8.30 Hz, 4H), 7.39 – 7.31 (m, 7H); ^{13}C (100 MHz, DMSO-d_6) δ 163.9, 161.4, 145.4, 129.0, 127.9, 127.8, 127.4, 127.3, 116.2, 116.0; HRMS (ESI) cacld for $C_{21}H_{14}ClFN_2$ $[M + H]^+$ 349.0912, found 349.0912.

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3l): a white solid; mp 230 – 233 °C; IR (cm^{-1}): 3429, 3032, 2940, 1601, 1481; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.07 (d, J = 5.91 Hz, 2H), 7.55 (d, J = 7.14 Hz, 2H), 7.48 (d, J = 7.14 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.31 (t, J = 7.45 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.08 (t, J = 7.45 Hz, 1H), 3.93 (s, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 156.5, 143.7, 136.9, 135.8, 131.7, 130.2, 129.3, 129.1, 129.0, 128.6, 128.1, 127.9, 127.6, 126.9, 121.1, 119.4, 112.1, 56.0; HRMS (ESI) calcd for $C_{22}H_{18}N_2O$ $[M + H]^-$ 325.1341, found 325.1345. Data consistent with literature.[26]

2-(2-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3m): a white solid; mp 238 – 241 °C; IR (cm^{-1}): 3453, 3058, 1602, 1484, 1220, 1101, 695; ^1H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.02 (t, J = 7.80 Hz, 1H), 7.54 – 7.33, (m, 13H); ^{13}C (100 MHz, DMSO-d_6) δ 160.6, 158.1, 141.3, 141.3, 131.4, 130.9, 130.8, 130.1, 130.1, 129.6, 129.0, 128.3, 127.6, 127.1, 125.1, 125.1, 119.2, 119.1, 116.8, 116.6; HRMS (ESI) calcd for $C_{21}H_{15}FN_2$ $[M + Na]^+$ 337.1117, found 337.1114. Data consistent with literature.[23]

2-(2-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3n): a yellow solid; mp 229 – 232 °C. IR (cm^{-1}): 3397, 3031, 1601, 1524, 1351, 1143, 693; ^1H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.00 (d, J = 8.51 Hz, 1H), 7.93 (d, J = 7.09 Hz, 1H), 7.79 (t, J = 7.44 Hz, 1H), 7.65 (t, J = 7.80 Hz, 1H), 7.51 (d, J = 7.80 Hz, 4H), 7.39 – 7.25 (m, 6H); ^{13}C (100 MHz, DMSO-d_6) δ 148.8, 141.5, 132.6, 130.3, 129.9, 129.4, 129.2, 128.9, 128.8, 127.6, 124.5, 123.9; HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M + H]^+$ 342.1243, found 342.1248. Data consistent with literature.[23,26]

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3o): a yellow solid; mp 281 – 285 °C. IR (cm^{-1}): 3394, 3057, 1520, 1347; ^1H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.97 (s, 1H), 8.51 (d, J = 8.01 Hz, 1H), 8.20 (d, J = 8.35 Hz, 1H), 7.77 (t, J = 8.02 Hz, 1H), 7.55 (d, J = 7.47 Hz, 4H), 7.40 (brs, 6H); ^{13}C (100 MHz, DMSO-d_6) δ 148.8, 143.9, 132.3, 131.6, 130.8, 129.4, 128.9, 128.7, 128.2, 123.0, 119.9; HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M + Na]^+$ 364.1062, found 364.1071. Data consistent with literature.[26]

2-(Furan-2-yl)-4,5-diphenyl-1*H*-imidazole (3p): a brown solid; mp 237 – 239 °C; IR (cm^{-1}): 3023, 1601,

1500, 1485, 739, 695; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 8.06 (d, 2H), 7.81, (s, 1H), 7.54 – 7.48 (dd, J = 7.16 Hz, 4H), 7.43 (t, J = 7.78 Hz, 2H), 7.37 (t, J = 7.37 Hz, 1H), 7.31 (t, J = 7.37 Hz, 2H), 7.23 (t, J = 7.37 Hz, 1H), 6.98 (d, J = 3.41 Hz, 1H), 6.66 (s, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 146.2, 143.5, 139.1, 137.5, 135.4, 131.3, 129.1, 128.8, 128.7, 128.3, 128.0, 127.6, 127.1, 112.3, 107.9; HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M + Na]^+$ 309.1861, found 309.1007. Data consistent with literature.[24]

2-Cyclohexyl-4,5-diphenyl-1*H*-imidazole (3q): 2-Phenylacetophenone (98.12 mg, 0.5 mmol) and selenium dioxide (55.48 mg, 0.5 mmol) were reacted under glacial acetic acid (5.00 mL) in an elongated tube equipped with a reflux condenser and a stirrer bar magnet for 3 h at 180 °C. Subsequently, cyclohexanecarboxaldehyde (60.57 µL, 0.5 mmol) and ammonium acetate (385.4 mg, 5.0 mmol) were directly added into the reaction mixture and allowed to react for another 3 h at 180 °C. After cooling, the ultimate reaction mixture was added dropwise into a 25% ammonia solution at 0 °C to form a white precipitate which was then filtered and dried in oven at 50 °C for 4 h to afford 2-cyclohexyl-4,5-diphenyl-1*H*-imidazole as a brown solid (133.30 mg, 83%); mp 243 – 245 °C. IR (cm^{-1}): 3031, 1603; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.50 (d, J = 7.94 Hz, 2H), 7.42 (q, J = 7.19 Hz, 4H), 7.26 (m, 3H), 7.17 (t, J = 6.95 Hz, 1H), 2.71 (m, 1H), 1.97 (d, J = 11.61 Hz, 2H), 1.79 (d, J = 12.44 Hz, 2H), 1.68 – 1.56 (m, 3H), 1.42 – 1.23 (m, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 152.9, 136.3, 135.5, 132.1, 129.0, 128.5, 128.3, 127.6, 127.5, 126.5, 126.2, 37.7, 32.0, 26.2; HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M + H]^+$ 303.1861, found 303.1869. Data consistent with literature.[25]

SUPPLEMENTARY INFORMATION

Experimental details, characterisation and copies of spectroscopic data can be accessed in the "Supplementary Information" of this article's webpage.

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